CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-853

21-654s016

CHEMISTRY REVIEW(S)

NDA 21-654
NDA 21-853

Omacor (omega-3-acid ethyl esters) Capsule

Ross Products Division – Abbott Laboratories, Inc.

Martin Haber, Ph.D.
Division of Metabolism and Endocrine Drug Products

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Chemistry Review Data Sheet

1. NDA 21-654 and 21-853

2. REVIEW #: 1

3. REVIEW DATE: October 20, 2004

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Initial Filing Memorandum	3/24/04
IR Letter	8/17/04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	1/9/04
Amendment	5/10/04
Amendment	7/1/04
Amendment	7/20/04
Amendment	9/3/04
Amendment	9/8/04
Amendment	9/10/04
Amendment	9/24/04
Amendment	9/29/04
Amendment	10/5/04

7. NAME & ADDRESS OF APPLICANT:

Name:	Ross Products Division Abbott Labs, Inc.
Address:	625 Cleveland Avenue, Columbus, OH 43215-1724
Representative:	Elizabeth M. Zola, Associate Director, Regulatory Affairs
Telephone:	614 624-3316

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: **Omacor**
b) Non-Proprietary Name (USAN): omega-3-acid ethyl esters
c) Code Name/# (ONDC only): K85EE
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 (21-654); 6 (21-853)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Treatment of hypertriglyceridemia

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 1 gram

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
___x__SPOTS product – Form Completed

_____Not a SPOTS product

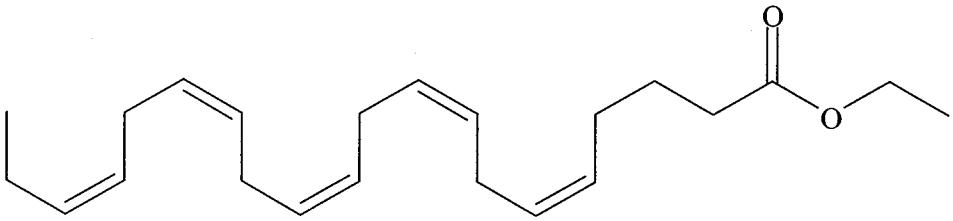
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Omega-3 acid ethyl esters is a fish-oil fatty acid ester concentrate containing about 46.5% all-cis (Z) 5,8,11,14,17-eicosapentaenoic acid ethyl ester (EPA-EE, C20:5n-3) and about 37.5% all-cis 4,7,10,13,16,19-docosahexaenoic acid ethyl ester (DHA-EE, C22:6n-3). Another approximately — consists of the ethyl esters of the following ⌐

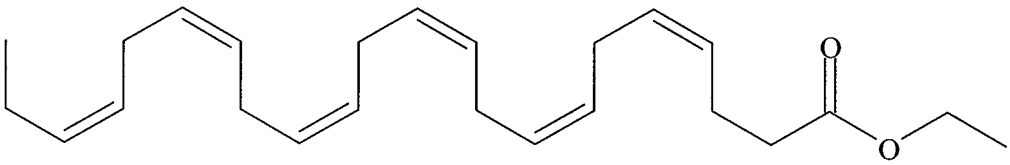
⌟ Also present at about — of the total mixture are the ethyl esters ⌐ b(4)

⌟ About 4 mg/g of α-tocopherol in partially hydrogenated vegetable oils is added to the drug substance as an antioxidant.

EPA ethyl ester: Formula: $C_{22}H_{34}O_2$ Molecular Weight: 330.51 CAS # 86227-47-6



DHA ethyl ester: Formula $C_{24}H_{36}O_2$ Molecular Weight: 356.55 CAS # 81926-94-5



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
14685	II	RP Scherer of North America	Soft Gelatin Capsule – Drug Product	1	Adequate	8/11/04	M. Haber
[redacted]	III	[redacted]		3	Adequate	7/27/04	S. Pope
[redacted]	III			3	Adequate	3/5/04	D.Chiapperino
[redacted]	III			3	Adequate	7/27/04	S. Pope

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	45,998	Fish Oils

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	AC	2/18/04	Dr. M. Haber
Pharm/Tox	NA		
Biopharm	AC	10/20/04	Dr. Wei Qiu
Methods Validation	Adequate, pending lab verification	10/20/04	Dr. M. Haber
DMETS	Tradename is acceptable	3/20/04	
EA	Categorical exclusion is acceptable	10/20/04	Dr. M. Haber
Microbiology	NA		

The Chemistry Review for NDA 21-654

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval from a CMC standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Omacor (omega-3-acid ethyl esters) is a soft clear gelatin capsule containing 1 gram of fish oil. There is only one strength marketed in 120-count plastic bottles. Omacor capsules also contain the following inactive ingredients: 4 mg α-tocopherol (antioxidant), gelatin, and traces of glycerol. Omacor is indicated for treatment of hypertriglyceridemia. The drug product capsules are manufactured by Cardinal Health, St. Petersburg, FL. Polyunsaturated fatty acids are susceptible to oxidation but the capsules are processed ⌜ ⌟ and the gelatin shell protects against oxidation. The capsules are stored in — bottles with plastic caps. The drug product capsules are stable at controlled room temperature for at least one year. b(4)

Omega-3 acid ethyl esters is a fish-oil fatty acid ester concentrate containing 46.5% all-cis (Z) 5,8,11,14,17-eicosapentaenoic acid ethyl ester (EPA-EE) and 37.5% all-cis 4,7,10,13,16,19-docosahexaenoic acid ethyl ester (DHA-EE). Another — of the drug substance consists of a mixture of the ethyl esters of ⌜

⌟ Also present at — of the total are the ethyl esters of ⌜ ⌟ The drug substance is produced by Pronova Biocare a.s., Norway, in a ⌜ ⌟ process involving ⌜ ⌟ from fish body oil. The oil is extracted from ocean fish families such as *Engaulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae* and *Scrombroidae*. The purification process ⌜ b(4)

⌟ The drug substance is stable for up to — when stored under — at room temperature.

B. Description of How the Drug Product is Intended to be Used

The recommended dose is 4 grams per day taken orally as a single dose (4 capsules) or as two 2-g doses. Patients should be on a lipid-lowering diet. The drug product consists of soft gelatin capsules containing 1 gram of omega-3-acid ethyl esters. The soft gelatin capsules are stored at controlled room temperature for up to 12 months in 120-count plastic bottles and caps.

C. Basis for Approvability or Not-Approval Recommendation

The quality of the drug substance, omega-3 acid ethyl esters, is adequate. The structures of the principle components, eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester, were determined by [ ] The reference standards are appropriate and adequate. The manufacturing process is adequate and well-controlled. The drug substance is prepared by [ ]

b(4)

The specifications for identity, assay, purity and consistency are adequate to assure the quality of the drug substance. Impurity testing includes tests for [ ] Additional information regarding the fatty acid distribution was added to the specifications. The drug substance is susceptible to oxidation and 0.4% α-tocopherol is added to the bulk as an antioxidant. The drug substance is stored in [ ] The stability of the drug substance has been demonstrated to be adequate at room temperature for up to [ ] without significant degradation in the absence of oxygen.

The quality of the drug product, Omacor Capsules, is adequate. The soft gelatin capsule drug product contains no excipients other than the antioxidant α-tocopherol and components of the capsule shell, gelatin and glycerin. The manufacturing process involves [ ]

The specifications are similar to those used for the drug substance and are adequate to assure the quality of the drug product. The drug product capsules are packaged in 28-count physician sample [ ] bottles and 120-count market [ ] bottles with plastic caps. Stability data submitted for the drug product capsules in bottles supports an expiration date of one year stored at room temperature. The cGMP status of all manufacturing facilities is satisfactory as per EER on 2/18/04. The firm has responded adequately to all CMC information requests and comments. There are no pending CMC deficiencies.

b(4)

III. Administrative

A. Reviewer's Signature — See DFS.
B. Endorsement Block — See DFS
C. CC Block — See DFS.

46 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Martin Haber
10/21/04 11:36:44 AM
CHEMIST

Mamta Gautam-Basak
10/21/04 11:55:23 AM
CHEMIST
Concur

NDA FILEABILITY CHECKLIST

NDA Number: 21-654 Applicant: Ross Products/Abbott Stamp Date: 1/12/04
Drug Name: Omacor (omega-3-acid ethyl esters) Capsules, 1 gram

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		Acceptable EER received.
6	Has an environmental assessment report or categorical exclusion been provided?	x		Exclusion is requested.
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		Final dissolution testing is not included.
9	Has stability data and analysis been provided to support the requested expiration date?	x		Only 6 months data is given on 3 production batches but the firm is requesting [redacted] expiry. Supportive stability data out to [redacted] years is available. b(4)
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		
14	Is there a Methods Validation package?	x		Dissolution development report is included.
15	Is a separate microbiological section included?			This is not needed because the dosage form is a capsule.

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist: M. Haber Date: March 11, 2004
Team Leader: M. Gautam-Basak Date: March 18, 2004
cc:

HFD-510/Division File

NDA Number: 21-654 **Applicant: Ross Products** **Stamp Date: 1/12/04**

Have all DMF References been Identified?

DMF Number	Holder	Description	LOA Included	Status
14685	Cardinal Health	Type II, drug product	Yes	**Pending**
15135	Cardinal Health	Type III, packaging	Yes	**Pending**
			Yes	Adequate, Reviewed by Dr. D. Klein
			Yes	Adequate, Reviewed by Dr. D. Klein
			Yes	Adequate, Reviewed by Dr. D. Klein
			Yes	Adequate, Reviewed by Dr. D. Lin
			Yes	Adequate, Reviewed by Dr. D. Christodoulou

b(4)

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Drug Substance

The active pharmaceutical ingredient is omega-3-acid ethyl esters. It is a purified, [ ] mixture of the desired fatty acid ethyl esters containing 0.4% of α-tocopherol as an anti-oxidant. The fatty acids are isolated from the body oil of fatty fish species such as *Engraulidae*, *Carangidae*, *Clupeidae*, *Osmeridae*, *Salmonidae* and *Scombridae*. b(4)

Site of manufacturing is Pronova Biocare a.s, Sandefjord, Norway.

The drug substance (K85EE) contains about 46.5% eicosapentaenoic acid (EPA, C20:5 n-3) and 37.5% docosahexaenoic acid (DHA, C22:6 n-3). The total amount of omega-3-acid ethyl esters [ ] is not less than [ ] b(4)

[ ] b(4)

PRONOVA BIOCARE

Specification

Product: K85EE	Specification no.: [ ]	Previous specification no.: [ ]	
This edition approved: 220803	Previous edition approved: 160503	First edition approved: 050900	Shelf life/retest period: [ ]
Prepared by: [ ]	Verified by: [ ]	Authorized by: [ ]	

b(4)

Test	Min. value	Max. value	Unit	Method
[ ]				

b(4)

PRONOVA BIOCARE

Specification

Product: K85EE	Specification no.: [redacted]	Previous specification no.: [redacted]	
This edition approved: 220803	Previous edition approved: 160503	First edition approved: 050900	Shelf life/retest period: —
Prepared by: [redacted]	Verified by: [redacted]	Authorized by: [redacted]	

Test	Min. value	Max. value	Unit	Method
[redacted]				

b(4)

b(4)

Drug substance stability is adequate. Data is provided for two lots for 12 months and one lot for six months. The retest period for the drug substance [redacted] at temperatures not to exceed 25°C.

b(4)

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PRONOVA BIOCARE

Specification

Product: Omacor capsules 1g USA	Specification no.: [redacted]	Previous specification no.: [redacted]	
This edition approved: 121203	Previous edition approved: 051203	First edition approved: 090998	Shelf life/retest period: 00000 days
Prepared by: [redacted]	Verified by: [redacted]	Authorized by: [redacted]	

Test	Min. value	Max. value	Unit	Method

b(4)

b(4)

One packaging configuration: [redacted] b(4)
Commercial 120 capsules/bottle
Physician's sample 28 capsules/bottle

Primary Stability Data:
Three commercial scale batches packaged in —— bottles: b(4)

25°C/60% RH	(1, 3, 6, months)
30°C/60% RH	(6 months)
40°C/75% RH	(1, 3, 6 months)

[redacted] b(4)

[redacted] Stability is good with no trend in assay values.

Supportive Stability Data for 36 months at room temperature and 6-12 months at accelerated temperature is given. There are two differences between the capsules used for these studies and the planned domestic manufacture. [redacted] b(4)

[redacted] Stability out to 36 months is good.

The sponsor has proposed an expiration-dating period of 3 years at 25°C.

EA: The firm has requested a categorical exclusion.

Draft Initial Filing Comments (for 74-day Letter):

1. Provide an estimate of the amounts of all impurities with identification as far as is possible. Provide the GC chromatograms with tabulated area percent for each peak for representative batches of drug substance and product and for reference standards.

2. Provide representative certificates of analysis for starting materials, including the crude fish oils. Define '[redacted]' more precisely. b(4)

3. Provide a brief description of the production of fish oil from whole fish.

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/s/

Martin Haber
3/24/04 02:52:28 PM
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Mamta Gautam-Basak
3/25/04 08:01:49 AM
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